The living state and cancer

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Abstract The surrounding world can be divided into two parts: alive and inanimate. What makes the difference is the subtle reactivity of living systems. The difference is so great that it is reasonable to suppose that what underlies life is a specific physical state, 'the living state'.

Living systems are built mainly of nucleic acids and proteins. The former are the guardians of the basic blueprint while the business of life is carried on by proteins. Proteins thus have to share the subtle reactivity of living systems. A closed-shell protein molecule, however, has no electronic mobility, and has but a low chemical reactivity. Its orbitals are occupied by electron pairs which are held firmly. The situation can be changed by taking single electrons out of the system. This unpairs electrons, leaves half-occupied orbitals with positive electron holes, making the molecules into highly reactive paramagnetic free radicals. The reactivity of the system depends on the degree of its electronic desaturation. Electrons can be taken out of protein molecules by 'electron acceptors' in 'charge transfer'.

When life began, our globe was covered by dense water vapour. There was no light and no free oxygen. Electron acceptors could be made out of trioses by concentrating their carbon atoms as carbonyls at one end of the molecule. The resulting methylglyoxal is a weak acceptor which made a low level of development possible. When light appeared, free oxygen was generated by the energy of photons. Oxygen is a strong electron acceptor. Its appearance opened the way to the present level of development. The transfer of electrons from protein to oxygen is effected by a complex chemical mechanism which involves ascorbic acid.

What is life? This is the main problem of biology. Many have asked this question, but nobody has answered it. Science is based on the experience that nature answers intelligent questions intelligently, so if she is silent there may be something wrong about the question. The question is wrong because life, as such, does not exist. What we can see is material systems which have this wonderful quality of being alive. What is this quality? This is the problem. It must be a very fundamental quality because it allows us to divide the whole surrounding world into two parts: 'animate' and 'inanimate', alive and not-

alive. The division is sharp and unequivocal, which suggests that the *living state* is a special physicochemical state, a state which can be described in terms of exact sciences and has to fit into the great order of the universe, having been created by the same forces as the universe itself. We must search for an understanding and an answer to our question with a wide natural philosophical outlook and fit life into the great scheme of creation.

What makes the difference between 'animate' and 'inanimate' is the wonderful subtle reactivity and flexibility of the animate. So our first question has to be: where to look for the physical basis of this reactivity, in what substance? The two main components of our body are nucleic acids and proteins. The nucleic acids are the guardians of the basic blueprints of structure, while the business of life is carried on by the proteins. So we can expect the proteins to share the subtle reactivity of life. Proteins are macromolecules, built from simpler constructional units: the amino acids. I could never believe that the wonderful subtlety of biological reactions should be brought about by clumsy, relatively unreactive macromolecules without the concurrence of much smaller and more mobile units which could hardly be anything else than electrons. But electrons are mobile only on a conductor and so, more than 30 years ago (1941), I proposed that proteins may be conductors. As far as any attention was given to it, my proposition was unanimously rejected. It was pointed out to me that already a large number of proteins have been isolated and thoroughly studied, none of which showed any signs of electrical conductivity.

This was a powerful argument and nothing could be said against it, but as time went by it became clear to me that science had overlooked here a very important circumstance: that proteins are the most versatile substances capable of performing the most different functions. On first approach, we have to distinguish between two kinds of functions: very simple ones which can be performed by single molecules in molecular dispersion, and more complex ones which can be performed only by integrated systems of molecules. These latter perform the great biological functions by which we know life, like motion and secretion or nervous activity. Such integrated systems have to be, by definition, insoluble. The simple primitive functions, like maintenance of osmotic pressure, or enzymic activity, which could be performed by single molecules in solution, in molecular dispersion, demanded no electronic mobility. But only these simple molecules were readily soluble, and for their analysis the protein chemists needed solutions. So what they did was to extract from tissues the soluble proteins, call the extracted tissue '*the residue*', and send it down the drain. With them they sent down the systems responsible for the higher biological functions, which had complex electronic structures.

If we were able to detach the integrated proteins that perform the vital functions, extract, precipitate, purify and crystallize them, I doubt whether they would still have the subtle qualities which characterize life and could tell us the difference between 'animate' and 'inanimate'.

Having decided to focus on proteins our next question is: in what dimension to search? Present-day biology is a *molecular biology,* which searches for answers mainly in the molecular dimension. Our body is built of molecules, so its reactions have to be molecular reactions, but molecules are built of atoms, and atoms are built of nuclei and electrons. So there is another dimension below the molecules which has been disregarded by biology.

The electrons surrounding the nuclei are in 'orbitals' which, in a way, can be looked on as boxes containing electrons in pairs. The two electrons of the pairs spin in opposite directions, compensating each other's magnetic moments, which makes them coupled. The electron pairs in their boxes are held firmly, have no mobility or high reactivity. In inanimate systems all these boxes in the ground state are occupied, making 'closed shell molecules'. An electron placed on such a molecule would find no place to go to. Shockley (1950) compared such a closed shell molecule to a completely filled parking lot to which no car could be added and in which the cars would have no mobility. It is difficult to see how such a clumsy closed shell molecule could produce the subtle reactivity of living systems. A molecular reaction between two of them would mean only sharing a superficially-lying electron pair. So the question arises whether there is a possibility of transforming such a clumsy unreactive macromolecule into a highly reactive unit with a measure of electronic mobility.

Returning to Shockley's parking lot, if we take out one single car we could make all other cars mobile, and having created an empty place we make shuffling possible. By taking out a single electron from the closed shell molecule we could create a 'positive hole' in it, opening the way to the shuffling of electrons. Taking out single electrons we also have to uncouple electron pairs and leave the earlier partner of the eliminated electrons with an uncompensated magnetic moment behind. A molecule containing such uncoupled electrons is a 'free radical', and radicals are known to be very reactive. We have upset the balance of the whole molecule. It seems natural that the more single electrons we take out, the more we upset the balance and make all electrons more mobile and reactive. By desaturating the molecule electronically we also do something very important, discovered lately by Laki & Ladik (1976): we greatly increase the interaction between the molecules. These forces which hold structures together are usually summed up as 'van der Waals attractions'. By desaturating the molecule, we thus strengthen the forces by

which molecules can be linked together to give higher and more complex structures capable of increasingly complex and subtle reactions: we have opened the way to development and differentiation, opened the way to evolution. Without desaturation, these forces are very weak and could not hold structures together against normal molecular agitation. This leads us to the first rule of electrobiology: *the living state is the electronically desaturated state of molecules, and the degree of development and differentiation is a function of the degree of electronic desaturation.* Electronic desaturation is a central problem of biology, and so the next sections will be devoted to the chemical mechanism of this process.

CHARGE TRANSFER AND PERMITTIVITY

Electrons can be taken out of molecules by other molecules by means of 'charge transfer'. If two molecules are held close together so that their orbitals overlap, the two form a single electronic system in which the electrons can rearrange themselves. If an electron in molecule A can decrease its free energy and increase its entropy by going over to molecule B, it will tend to do so, leaving its own molecule behind with a positive charge. Molecule A becomes a donor, while the 'acceptor' molecule B acquires a negative charge. The transfer of a whole electron to another molecule, where it stays put, is a rare event which occurs only in 'strong' charge transfer. What mostly will happen is that the transferred electron or electrons oscillate between the two molecules. Depending on various factors the oscillating electrons may not divide their time equally between the two molecules but may spend, say, 1% more on A than on B. It is customary to say, in such a case, that only one hundredth of an electron has been transferred. Such a partial transfer of electrons may play a very important part in biology and contribute to the subtle adjustment of biological reactions. It may have also a major importance for the mechanism of evolution.*

Here we meet a difficulty: by transferring an electron we create two electrically charged free radicals (Fig. 1: A and B). Electrically charged free radicals are exceedingly reactive and it is doubtful whether this reactivity is compatible with life. There is a way out. Let us suppose that before transferring the electron from B to A we incorporate B into A, as shown in Fig. 1C. In this case the transfer of electrons could take place as before and transform both molecules into reactive free radicals, but no net charge would be

*It is believable that by sending out 'fractions of electrons', molecules could explore simultaneously a number of situations and would stay only where they can decrease their free energy, increase their entropy and do something useful.

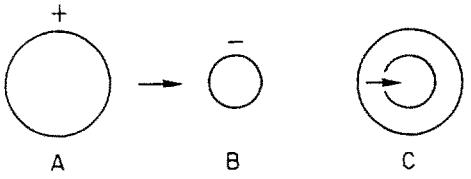

FIG. 1. A and B symbolize charge transfer; C stands for doping.

generated, the transfer having taken place inside the complex. Such incorporation with intramolecular charge transfer is called 'doping', which is one of the most important reactions on which the electronics industry is built, in which poor semiconductors are made into strong ones by doping them with electron donors or acceptors.

The creation of life demanded 'donors' and 'acceptors'. How do we find them? The universe has been transformed into one coherent system by the periodic chart of atoms of Mendeleev, the top rows of which are reproduced in Fig. 2. Where do donors and acceptors fit into this system? As we all know, this chart, which contains all the elements, consists of horizontal and vertical rows. Each horizontal row begins and ends with a noble gas. The noble gases are the most stable ones, and all physical systems tend to acquire stability. So all elements tend to resemble a noble gas by having the same number of electrons in their outermost shell. The elements on the right side of the chart have less, those on the left side have more electrons than the nearest noble gas; and so the former tend to take up electrons and the latter tend to give off electrons. Thus the former become electron acceptors, the latter electron donors. According to the table the best acceptors are fluorine and the other halogens. In fact, they are too strong as acceptors to be used by life, so for a good biological acceptor we have to turn to the next column, headed by oxygen, the universal biological acceptor. The energy driving life is derived from the transfer of an electron from hydrogen to oxygen.

Charge transfer depends to a great extent on the dielectric constant, ϵ, of the solvent, which decides its permittivity. A high ϵ corresponds to a high permittivity, and a low ϵ to a low permittivity. A given ϵ may both promote and impede charge transfer in which positive and negative charges have to be separated. Such separation will be promoted by a high ϵ which depolarizes the charges and so facilitates separation. At the same time, for charge transfer to take place, the two interacting molecules have to be held together in close proximity by conventional forces which are electropolar. So a high ϵ

	H							
He	Li	Be	B	C	N	O	F	Ne
Ne	Na	Mg	Al	Si	P	S	Cl	Ar

FIG. 2. Top lines of Mendeleev's periodic chart of atoms. To make the figure correct it would have to be cut out and rolled into a spiral in which the two neons overlap.

will tend to depolarize and disrupt such complexes, interfering with charge transfer. One special case of complex formation is dimerization (or polymerization in general), which can greatly promote charge transfer, as shown in Fig. 3. In Fig. 3, A represents a charge transfer complex in which the charges have been transferred to the ends of the particle. A dimerization, as shown in B, will greatly depolarize and so facilitate the transfer. These opposing influences will allow some charge transfer to take place only at a certain ϵ where the opposing forces balance each other most favourably. This is illustrated in Fig. 4, in an experiment in which a series of test tubes were filled with different solvents containing an increasing amount of water, the concentration of water increasing from tube to tube by 10%. The far left tube contained the pure organic solvent and the last one on the right, pure water. Then in all tubes a charge transfer reaction was performed which could be recognized by its colour. The + sign indicates the intensity of colour and charge transfer. The organic solvents had a relatively low ϵ (45 for dimethyl sulphoxide and 37 for dimethylformamide). As can be seen in Fig. 4, there was no reaction in the pure organic solvents; the reaction gradually became stronger as the ϵ increased, then weaker again in pure water.

As will be discussed later, I believe that cancer, essentially, is a failure to desaturate proteins and so substances which interfere with charge transfer have to be carcinogenic. According to Fig. 4, water is a carcinogen. This car-

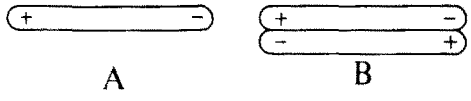

FIG. 3. A. A fibrous molecule with separated charges. B. The same dimerized. The figure is intended to show that the separation of charges promotes dimerization and dimerization promotes the separation of charges.

DIMETHYLSULFOXIDE	0	±	(+)	+	++	+++	++	+	+	±	±
DIMETHYLFORMAMIDE	0	(±)	±	+	(++)	++	++	++	+	(+)	±
GLYCEROL	+++	++++	++++	++++	++++	+++	+++	++	++	+	±

FIG. 4. Intensity of the charge transfer reaction between methylamine and methylglyoxal in a mixture of dimethyl sulphoxide or dimethylformamide and water. The first sample on the left contains the pure organic solvent, the last on the right, pure water. The maximum of the reaction is around $\epsilon = 60$. Glycerol (bottom line) has no such maximum.

cinogenic activity of water around the living protein structure is eliminated by the water structures the proteins build around themselves, which decrease ϵ. The ϵ of water is 81.5; that of ice is 2, similar to that of paraffin wax.

The third line in Fig. 4 shows glycerol. I showed many years ago (1949) that the motility of muscle can be preserved for years in 50% glycerol. Up to now this activity has been mystery. It seems to be the result of the favourable permittivity of the solvent, which allows the conservation of electronic relations.

METHYLGLYOXAL

When life originated, about three and a half billion years ago, it was probably pitch dark on our globe and there was no oxygen, the earth being covered by a dense layer of water vapour. There was no free oxygen. The oxygen was present in bound form as water, carbonate, phosphate, etc. which is of no use as an acceptor for protein. So if our rules of electronic biology are valid and there can be no life without desaturation, and oxygen is the universal acceptor, then we have to suppose that life found ways of using the bound oxygen as acceptor. Nature achieved this by taking a molecule of water out of triose and crowding all the oxygens as carbonyl, C=O, at one end of the molecule, the hydrogens at the other. The substance formed is methylglyoxal (Fig. 5).

Nature is simple but subtle (P. Ehrenfest, personal communication). Methylglyoxal is a unique substance. There is no other substance with its special characteristics. In spite of its small size it contains a reactive aldehydic group, and a ketonic C=O, which has a low lying triplet orbital (Abdulnur 1976), making it an acceptor. Triose is the smallest molecule which could be transformed in this way.

That I have not lost myself in meaningless speculation and am still close to the central problems of biology is indicated by the fact that more than sixty years ago a most reactive and apparently ubiquitous biological enzymic

system was discovered, *'glyoxalase'*, which catalyses a two-step reaction using glutathione as coenzyme. It can transform, at an extreme speed, methylglyoxal into D-lactic acid. Nature does not indulge in luxuries, and if there is such a widely spread and active enzymic system, it must have something very important to do. But up to the present nobody has been able to find any use for it, D-lactic acid and methylglyoxal not being known to have any major biological function.

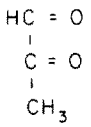

FIG. 5. Structure of methylglyoxal.

Methylglyoxal can attack protein by means of its aldehydic C=O interacting with an amino group of protein. Protein has but one typical NH_2 group which is in its lysine residues.* Before discussing this interaction I should like to consider briefly a simpler model in which the protein's place is taken by the simplest aliphatic amine, methylamine.

If aqueous solutions of methylamine and methylglyoxal are mixed, the appearance of a yellow colour indicates the formation of a Schiff base which contains the chromogenic N=C link:

$$R^1-C=O + H_2N-R^2 \rightarrow R^1-C=N-R^2 + H_2O$$

If the same reaction is performed in a solvent of lower permittivity, such as methanol or acetone, instead of water, a purple colour appears. If 0.5M-acetone solutions of two reagents are mixed, then the purple product precipitates and can be isolated. Pohl *et al.* (1977) measured its molecular weight, which indicated a polymerization to a tetramer. In the electron spin resonance (e.s.r.) spectroscope the purple precipitate gives a strong signal with a rich hyperfine structure, showing that polymerization and charge transfer have occurred. In the first instance the precipitate is colourless; it turns purple in a fraction of a second, showing that the primary product of the reaction is a colourless substance. The same can be shown also for the Schiff bases by using butylamine instead of methylamine. The colourless primary product is in

*The NH_2 in arginine residues is part of a guanidine group and has specific qualities and reactions.

all probability a hemiacetal.* At the high permittivity of water the hemiacetal turns into the yellow Schiff base, while at a lower permittivity, such as that of acetone or methanol, it polymerizes and turns into the purple charge transfer complex.

METHYLGLYOXAL AND PROTEIN

If we represent the peptide chain of protein by a straight line, as has been done in Fig. 6, then the lysine side-chain can be drawn as a straight line which hangs out to one side, consisting of four carbon atoms with an NH_2 at its end. This side-chain can be looked upon as a fishing rod, fishing for methylglyoxal. Methylglyoxal molecules can be expected to attach themselves to the amino group forming a Schiff base which is but slightly weaker as an acceptor than methylglyoxal (J. Ladik, unpublished calculations).

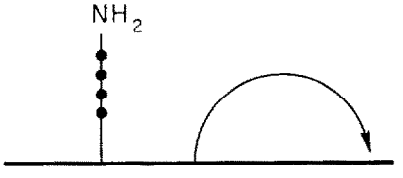

FIG. 6.

While the lysine side-chain is stretched out it can take with its Schiff base no electrons from the peptide chain from which it is separated by four saturated carbon atoms, through which no electrons can be transmitted. However, the side-chain is pliable and can fold. Otto *et al.* (1978) made a thorough study of this folding and found that it will bring the Schiff base into touch with the second-neighbour peptide bond of the peptide chain of the protein, enabling it to enter a charge transfer reaction with it and take electrons from it. It will form an n-p junction which will charge the Schiff base negatively, the peptide chain positively, making it into a p-type conductor.† In many proteins, about

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*$CH_3-NH_2 + O= \underset{\underset{R}{|}}{C}-H-CH_3-\underset{\underset{H}{|}}{N}-\underset{\underset{R}{|}}{\overset{\overset{H}{|}}{C}}OH$

†It deserves consideration whether anaerobic life may not be based on an n-type conductivity. The very first forms of life had to be anaerobic.

each eighth amino acid residue is a lysine (Fig. 7), and so the peptide chain has a boosting station at every eighth amino acid. This lysine side-chain with the attached Schiff base is the kernel of the mechanism proteins carry with them for their desaturation.

If a solution of lysine is treated with methylglyoxal it turns yellow because of the formation of a Schiff base. It can give no purple complex, not even in alcohol or acetone, because the bulky molecule interferes with polymerization. If a protein, such as casein, is treated with aqueous methylglyoxal, its granules being suspended in methylglyoxal solution, it turns yellow, but if the amino groups of the lysine residues are methylated, the protein remains colourless. If treated with a methanol solution of methylglyoxal, the colour of the protein becomes darker, brown. Since the lysine side-chains cannot polymerize this darker colour has to be due to a more intimate complexing of the Schiff base with the peptide chain, due to the lower permittivity of the solvent.

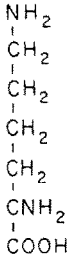

FIG. 7. Lysine.

The brown colour of the methylglyoxal-treated casein is very similar to that of the liver, which makes it seem likely that the liver actually owes at least part of its colour to its electronic desaturation by methylglyoxal. Fodor *et al.* (1978) have in fact isolated and identified the methylglyoxal linked to the liver protein.

In the first period, life had to be based on a desaturation by methylglyoxal, which is a weak acceptor, and so life, in this period, could have developed but only the simplest forms which have left no traces behind.

Fig. 6 suggests that the Schiff base, being at the end of the lysine side-chain, at a distance from the peptide chain, is formed in random water which promotes the formation of Schiff bases. The association of the Schiff base with the peptide link in the peptide chain may be promoted by the lowered dielectric constant, lowered by the protein, which builds water structures around itself.

According to the theory presented, the desaturation of the peptide chain should lead to an increase in its electronic conductivity. This conductivity has been measured by Pethig & Szent-Györgyi (1977) as well as by Bone *et al.* (1978) and found to be increased considerably.

The brown colour of the liver indicates unpaired electrons and suggests that protein radicals are an important part of the structure of liver cells. Pohl *et al.* (1977) isolated these coloured proteins and found them to be paramagnetic, giving a strong e.s.r. signal, similar to the signal given by casein treated with methylglyoxal. This suggests that the e.s.r. signals given by living material are actually due to the protein radicals composing the cellular structures, and are not entirely due to undefined free radicals in solution, as hitherto supposed. The structural proteins in Pohl's experiments were isolated by homogenizing the tissue in ice-cooled 50% ammonium sulphate and subsequent centrifugation. The soluble proteins were isolated similarly in the centrifuge by 100% saturation, after the structural proteins had been eliminated; the soluble proteins gave but a very weak signal.

THE α — β TRANSFORMATION

The history of life was divided into two parts by the appearance of light. In the first, dark period the globe was covered by dense water vapour, and the atmosphere had to be reducing. There was no free oxygen, and there could be no stable electron acceptors. Accordingly, life could reach only a very low degree of development, which has left practically no traces behind. The protein in this period had to be desaturated by methylglyoxal, which is a weak acceptor and could develop only the simplest forms of life, the main function of which had to be the proliferation which made life perennial. This unbridled proliferation had to be favoured by the low level of cohesive forces and the poverty and simplicity of structures. I have called this first dark proliferative part 'the α period'.

This situation changed when, because of cooling, the water vapour condensed and light could reach the surface of the globe. What life did with this light was to use its energy for the separation of the elements of water, producing oxygen, which is a strong acceptor, and so could start up the development and differentiation, the end result of which is us. I have called the second, light oxidative part of life's history the β period. The cohesive forces generated by the electronic desaturation led to the building of increasingly complex structures with increasingly complex and subtle reactions.

Cohesion and structures interfere with proliferation, so when the cell divides it has to lower its cohesive forces and dismount part of its structure.

These changes can be summed up as a partial return to the α state, which is the ground state of life. It has to be the more stable state, having the lower free energy and higher entropy. So the $\alpha \longleftrightarrow \beta$ transformation had to be kept reversible. After it had completed its division, the cell had to build up its β state again. So in the β period the unbridled proliferation was replaced by regulated growth. Should the cell, after completing cell division, find the way of return to the β state perturbed, it has to persist in the proliferative α state and continue to divide when no division is needed, leading to a tumour. This also explains why very rapidly dividing cells resemble one another, be they embryonic, cancerous, or simply very rapidly dividing normal cells.

The more complete the return to the α state, the faster the proliferation and the lower the cohesive forces will be, and the more malignant the tumour produced.

ASCORBIC ACID

Free oxygen, O_2, is a strong electron acceptor and so its appearance in the β period opened the way to a higher degree of electronic desaturation, and to the corresponding higher degree of differentiation and development. If nature develops a new method, as a rule, she does not throw the old one out, but simply adds the new one to it, improving it. So, in the β period, methylglyoxal was not replaced by O_2, but the O_2 was added to it, boosting up its acceptor strength.

However, oxygen does not interact with protein, nor does it interact with methylglyoxal. So in order for it to be used as an acceptor for protein, a link had to be developed by which the oxygen could be linked to methylglyoxal, transferring to it part of its acceptor power. This link had to have very specific qualities: it had to be able to make a bond simultaneously both with oxygen and methylglyoxal and had to have an electronic mobility by which it could transfer the acceptor strength of O_2 to the ketoaldehyde. This new substance, which nature developed when light and oxygen appeared, is ascorbic acid, discovered by me in the early thirties. Later it was found to have an antiscorbutic activity, and to be identical with the then unknown antiscorbutic component of fresh vegetables called 'Vitamin C'.

In a remarkably short time the chemical nature of ascorbic acid was cleared up and the substance became available at low cost in crystalline condition in an unlimited quantity. But while we have learned everything worth knowing about its chemistry, its biological function remained unknown, preventing medicine from making full use of its remarkable reactivity. We can control only what we understand. Even a simple question, such as the magnitude of

the recommended daily dose, has remained unsettled, oscillating between megadoses and a few milligrams.

The development of ascorbic acid is one of the landmarks of evolution, as was the appearance of light and oxygen. That ascorbic acid readily interacts with oxygen can be shown by placing a sample of its Na salt into the e.s.r. spectrometer in the absence of oxygen. On admission of air the typical free radical signal appears, consisting of a doublet with a splitting of 1.75 gauss. Each part of the doublet has a further triplet splitting of 0.175 gauss.

That ascorbic acid can readily interact with methylglyoxal has been shown by Fodor, who will describe his observations later in this symposium (Fodor *et al.*, pp. 165-169).

The great mobility of the unpaired electron inside the ascorbate radical can be demonstrated by e.s.r. which shows that this electron can interact with many of the protons of ascorbate.

Also, the spectrometer gives valuable information about the interaction of oxygen, ascorbate and methylglyoxal, which information has hitherto been utilized only to a small extent. If methylamine and methylglyoxal solutions are mixed a very strong signal appears with a rich hyperfine structure. In the presence of ascorbate the signal is much stronger, showing that the ascorbate catalyses charge transfer, without changing the character. If casein is treated with methylglyoxal in the presence of ascorbate, a new signal appears (P.C.R. Gascoyne, personal communication), indicating that the ascorbate is built into the charge transfer complex—an observation which may have far-reaching biological consequences and introduces new viewpoints into the medical use of the acid.

Most fascinating and complex spectroscopic reactions have been found by my colleague Jane McLaughlin (unpublished results). If both cuvettes of the spectrophotometer contained a mixture of a 0.0256M solution of methylglyoxal and methylamine (0.077M), and 0.0077M-ascorbic acid was added, a very strong absorption appeared around 400 nm, which disappeared slowly (Fig. 8). A second peak appeared around 500 nm. In the absence of oxygen the addition of ascorbic acid made no difference, showing that it catalysed the charge transfer between $O_2^{\cdot}$ and methylglyoxal. If no ascorbate was present, admission of oxygen to the mixture of methylglyoxal and methylamine inhibited the appearance of the absorption spectrum.

Oxygen, essentially, brings the life-giving light into the living system. Ascorbic acid catalyses this reaction. It is involved in bringing matter to life. This opens up new aspects of the medical application of ascorbic acid.

The actual role played by oxygen in these reactions is yet unknown and demands more study on the basic level. It is possible that the O_2 molecule

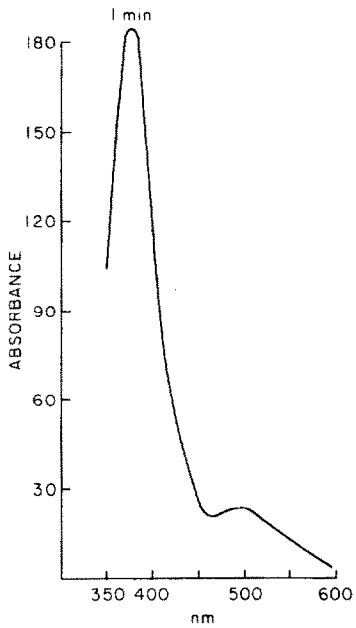

FIG. 8. See text for explantation (p. 15).

simply takes an electron over and dissociates off, but it seems more likely to me that it takes over only parts of an electron and remains attached to the charge transfer complex. If, in this case, the oxygen pressure is decreased, the oxygen may dissociate off, upsetting the electron balance in the whole charge transfer mechanism. This may explain why consciousness instantaneously fades out if the oxygen supply to the brain is cut off. This suggests also that in the comatose state after a heart attack the infusion of ascorbic acid and artificial respiration might be indicated.

A THEORY OF CANCER

Two cardinal symptoms of a cancerous transformation are a low paramagnetic susceptibility and a low cohesion. Both are the consequences of a defective desaturation of the structural proteins, due to the loosening up and disorganization of the chemical machinery, a shift towards the α state.

A cell is a strongly integrated system and all its reactions are coupled to one another. In the normal cell the reactions are coupled in such a way that activity improves activity. Desaturation promotes further desaturation, and exercise makes us stronger, but coupling is a two-way street, and factors which inhibit normal interactions may be coupled in such a way that they cause further

inhibition. An inadequate desaturation may inhibit desaturation. This can push the cell into a *vicious circle* which the cell is unable to break, and leads it into a state of disorganization, landing it in the proliferative α state. If the situation is not corrected this situation may become constitutive, irreversible.

To be able to correct a deficiency we need a still better and more detailed knowledge of the chemical machinery of electronic desaturation, which can be achieved by basic research. The blindfold search for a cure for cancer seems a hopeless waste. Until correction becomes possible the best defence against cancer is keeping the machinery in perfect working order. More than sixty years of research on living systems has convinced me that our body is much more nearly perfect than the endless list of ailments suggests. Its shortcomings are due less to its inborn imperfections than to our abusing it.

One factor which deserves special attention is ascorbic acid, for the supply of which we depend on food, the expensive nature of which is not a guarantee of its quality. Some experiments suggest that this acid is not merely a catalyst but that it is built into the machinery—and is part and parcel of it. Since we are building and rebuilding this machinery all the time, a continuous supply of ascorbic acid is important. A machinery built without ascorbic acid cannot be corrected by suddenly administering megadoses. Correction of defects may take the better part of a year.

The ideal of medicine is the curing of all diseases. The ideal should be full health, which leaves no room for any shortcoming. In the U.S.A. we are still losing the battle against cancer: every day there are eight hundred casualties. I strongly believe that cancer is accessible to a complete analysis on the basic level, and that understanding it means also the ability to control it.

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